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# Midlife Cardiovascular Risk Impacts Executive Function: Framingham Offspring Study

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## Abstract

**Introduction—***Novel error scores* and traditional indices of executive function (EF) were related to cardiovascular risk factors (CVRF) measured 10–15 years earlier.

**Methods—**From 1991–1995, the Framingham Stroke Risk Profile (FSRP), a composite score of cardiovascular risk, was ascertained in 1755 Framingham Offspring participants (54% women, mean age= 54 ± 9 years). Participants were administered EF tests: FAS and Animals Fluency tests, Trail Making Test B (TrB), and Digit Span-Backwards (DS-B) in 2005–2009. Linear and logistic regression were used to relate the FSRP and its components to both error responses and traditional scores.

**Results—**Consistent with previous findings, the FSRP and the individual components diabetes and sex were associated with several traditional measures of EF. Of interest were relationships between the FSRP score and TrB Total Errors (p=0.04), DS-B % Total Errors (p=0.02) and DS-B Capacity Score (p=0.03), and prevalent CVD related to making FAS Perseverations in the 75th percentile (p=0.03). By comparison, FSRP and CVD were not related to the traditional DS-B or FAS scores. Additionally, age was associated with higher Animals % Total Errors and % Perseverations among ApoE4+ individuals and with higher TrB Total Errors among ApoE4− individuals.

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**Conclusion—**For those middle-aged and healthy, including those ApoE4+, CVRF are related to impairments in EF as ascertained by novel errors as well as traditional measures.

### Keywords

Neuropsychological assessment; Executive function; Mild cognitive impairment; ApolipoproteinE allele 4

## Introduction

Previous studies have reported that high cardiovascular risk leads to increased risk of dementia in later life[1–5]. There is also some limited evidence suggesting a relationship between mid-life cardiovascular risk and later-life executive function (EF) impairment, among those who are not demented[6–15]. Recent studies examining mid-life cardiovascular risk and cognition have focused on individual risk factors[6,8,10–14], despite the fact that they often co-occur[16]. There is some consensus suggesting a relationship between mid-life systolic blood pressure and EF[6–9,11–15]. For other risk factors including diabetes and smoking, findings are mixed and may relate to methodological differences including length of follow-up, demographically diverse study samples, and variability in cognitive tests used[6–8,10].

There is continued reliance on neuropsychological (NP) test scores to detect dysfunction sufficient to meet criteria for dementia. With increasing interest in detection of cognitive impairments that significantly precede onset of clinical disease, it is important to consider additional measurements that may reflect changes in cognitive status. There is a particular need to determine whether subtle signs of mild cognitive impairment attributed to vascular risk factors can be identified[17,18]. Thus, we introduce error response measures of EF that capture differences in cognitive performance not reflected in traditionally collected measures.

The apolipoproteinE ε4 allele (ApoE4) has been shown to be associated with accelerated cognitive decline in cognitively normal populations[19–21]. Furthermore, ApoE4 may play a role in modifying the relationships between cardiovascular risk and cognition[22–26] although this finding has been challenged in the elderly[27].

This study examined the association between a composite score of cardiovascular risk, the Framingham Stroke Risk Profile (FSRP) score[28], and EF measured approximately 15 years later, using traditional EF measures as well as a new set of error response measures. We additionally examined whether ApoE4 modifies the relationship between FSRP and EF.

## Methods

### Study Sample

The Framingham Offspring Study cohort ($n$ = 5,124) is a community-based sample comprised of people who had a least one biological parent who was a member of the original Framingham Study cohort and their spouses[29]. Beginning in 1971, and repeated approximately every four years, this cohort has undergone a total of eight clinical examinations to identify risk factors for stroke and cardiovascular disease[29]. Our study sample was derived from the 2,037 Offspring participants who had participated in the fifth clinical examination (Exam 5, from 1991–1995) and had complete NP data from testing administered from September 1, 2005 through December 31, 2009. We excluded 128 participants for prevalent stroke, dementia, or other neurological disorders at the time of NP testing, 2 participants for missing education data, and 152 participants for missing

cardiovascular risk (FSRP) data from Exam 5, resulting in a final sample size of 1,755 (53.6% women; mean age at NP exam 67.2 years). The Boston University Institutional Review Board approved the study protocol and all participants provided written informed consent.

### Cardiovascular Risk and Covariate Assessment

All cardiovascular risk factors (CVRF) and covariates were measured at Exam 5. The FSRP is a composite score of CVRF that predicts 10-year probability of stroke based on age, gender, and specific cardiovascular risk factors[28,30]. These risk factors include systolic blood pressure (SBP), antihypertensive therapy (yes/no), diabetes (fasting plasma glucose of at least 126 mg/dL or report of treatment with insulin or an oral hypoglycemic agent), cigarette smoking status (yes/no), history of cardiovascular disease (CVD; history of coronary heart disease, congestive heart failure, or peripheral vascular disease), atrial fibrillation (AF), and left ventricular hypertrophy (LVH) that can be identified on an EKG[28]. The FSRP has been well-validated both within Framingham and by outside investigations[31,32]. The FSRP, measured at an average age of 53.6 years (SD = 9.1 years), was used as a measure of cardiovascular risk at mid-life, and the individual risk factors of current smoking, diabetes, hypertension, and prevalent CVD were considered separately. Hypertension was defined as reported use of antihypertensive medication or having a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg. Prevalent AF was not considered individually in our analysis because of its low prevalence in our study sample.

### Outcome Assessment: Measurements of Executive Function

A NP test battery was administered using standardized test procedures as described in previous FHS publications[6,33]. The following EF tests were included: Controlled Word Association Test (FAS), Category Naming (Animals), Halstad-Reitan Trailmaking Test B (Trails B), and Wechsler Memory Scale - Digit Span-Backwards (DS-B). Standard quantitative total scores for each were computed using traditional scoring methods. Additional scoring procedures characterizing error responses were also implemented.

For the FAS and Animals tests, the test administrator recorded the total number of correct responses (traditional measure) and the number of perseverations (e.g., repetition of a previous response), broken rules (e.g., loss of set), and wrong first letters (words that did not start with “F”,”A”, or “S”). For both the FAS and Animals tests, the error response measures included percent perseverations ((total number of perseverations/total number of responses) *100) and percent total errors (((total number of perseverations, broken rules, and wrong first letters (FAS only))/total number of responses) *100).

Trails B measure of EF was computed as the difference in total time to completion for Trails B minus Trails A (Trails B-A), in order to correct for motor speed and simple attention. Trails B-A was transformed so that higher values represent better performance, to be consistent with the other tests. In instances where non-completion of the Trails B test was attributed to cognitive inability to understand task instructions or loss of understanding of task requirements during the test, a maximum score of 300 seconds was assigned. Error response measures for Trails B included the total number of corrected errors (examiner or self), the number of pen lifts, and whether the individual started the test before she/he was told to begin.

For the DS-B test, the traditional measure was the highest correctly repeated span length. The test was also administered beyond the official discontinue point, as is commonly referred to as “testing the limits.”[34–36] The rationale is that as long as the person reported

correctly all the numbers presented, and produced only sequencing errors, the test was continued because actual span capacity had not been reached. Only after both trials of a particular span length were inaccurately repeated due to non-sequencing errors (e.g., omissions, substitutions, additions) was the test discontinued. The highest span length obtained under the "testing the limits" scenario was denoted as the DS-B limit, and DS-B capacity score was computed by taking the difference between the standard and the limit scores. Other novel error response measures included the percent total errors ((total sequencing and non-sequencing errors)/total number of trials *100), and the percent sequencing errors (total number of sequencing errors/total number or errors *100).

### Statistical Analysis

Linear regression was used to examine the associations between the FSRP score and its components and continuous EF variables. Continuous variables were natural log transformed to normalize their distributions, as necessary. All novel EF variables were dichotomized into $\geq 75^{th}$ percentile versus $<75^{th}$ percentile due to the skewed distribution of the variables. Logistic regression was used to examine the associations between the FSRP score and its components and categorical EF variables. All analyses were adjusted for age at NP testing, sex, education group (< High school degree, High school degree, College degree, >College degree), and time between FSRP measurement (Exam 5) and NP testing dates. The interaction between the FSRP score and its components and ApoE4 was assessed using a Wald test. A p-value of <0.05 was considered statistically significant. All statistical analyses were done using SAS version 9.2 (Cary, NC).

## Results

### Study Sample Characteristics

Table 1 shows the descriptive characteristics of the 1,755 participants included in the analysis. Overall the sample was ~54% women and had a mean age of 53.6 years (SD=9.1 years) at the baseline cardiovascular risk factor assessment. The participants underwent NP testing a mean of 14.1 years (SD=1.2 years) after the baseline risk factor measurements. Approximately 40% of the sample had at least a college degree and the mean MMSE score was 29.1 (SD=1.2) of a maximum of 30 points. The normative data for the error response variables of the executive function tests are described in a separate paper[37]. The mean and median scores for NP tests are also shown in Table 1.

### Association between Cardiovascular Risk Factors and Traditional NP Outcome Measures

Table 2 shows the association between the CVRF measures (i.e., the FSRP score and its FSRP component scores) and the traditional outcome measures from the NP tests.

There was a statistically significant inverse association between FSRP score and total number of responses on the Animals test. For each one percentage point increase in FSRP score, the total responses score on the Animals test decreased by 0.09 (Beta=−0.09, p=0.03). FSRP was also inversely associated with Trails B-A time to completion (Beta=−0.008, p=0.0002).

Examination of the individual components of the FSRP score, particularly age and sex, yielded significant associations with several of the traditional measures. Age was inversely associated with FAS total correct responses (Beta= −0.29, p<0.0001), Animals total correct responses (Beta= −0.21, p<0.0001), Trails B-A completion time (Beta=−0.01, p<0.0001), and the DS-B total score (Beta= −0.01, p=0.0003). Women had higher FAS total correct responses (Beta=3.0, p<0.0001) than men. Participants with diabetes had on average 3.3 fewer FAS total correct responses than those without diabetes (p=0.007). There were no

other statistically significant associations between the FSRP components and traditional outcome measures.

### Association between Cardiovascular Risk Factors and Error Response NP Outcome Measures

The associations between the FSRP score and its components and the error response NP outcome measures are shown in Table 3.

FSRP was positively associated with total Trails B errors (OR, p=0.04), DS-B capacity score (OR=1.05, p=0.03), and with DS-B % total errors (OR=1.05, p=0.02).

Among the individual components of the FSRP score, age was positively associated with FAS % perseverations (OR=1.04, p<0.0001), FAS % total errors (OR=1.04, p<0.0001), Animals % perseverations (OR=1.03, p=0.0003), Animals % total errors (OR=1.03, p<0.0001), Trails B total errors (OR=1.04, p<0.0001), number of Trails B pen lifts (OR=1.06, p<0.0001), and Trails B early start (OR=1.05, p =0.0001). Women had lower FAS % total errors (OR=0.70, p=0.003) and higher Animals % perseverations (OR=1.27, p=0.045) than men. Participants with prevalent CVD were less likely to have FAS % perseverations ≥75$^{th}$ percentile compared to those without prevalent CVD (OR=0.51, p=0.03). There were no other statistically significant associations between FSRP components and error response outcome measures.

### Interaction between ApoE4 Status and Cardiovascular Risk Factors on Traditional NP Outcome Measures

Table 4a shows the stratum-specific results for the statistically significant interactions between ApoE4 and the FSRP score and its components on the traditional NP outcome measures.

There was an interaction between ApoE4 and age on the total correct responses for the Animals test ($p_{interaction}$=0.03) and a stronger inverse association between age and total correct responses on the Animals test among those with the ApoE4 allele. There were also significant interactions between ApoE4 and hypertension on FAS ($p_{interaction}$=0.04) and Animals ($p_{interaction}$=0.03) total correct responses with a statistically significant inverse association present between hypertension and FAS total correct responses only among ApoE4 positive participants (Beta=−3.2, p=0.03).

While there was no statistically significant association between hypertension and Animals total correct responses among the ApoE4 negative group (Beta=−0.25, p=0.39), a significant positive association among the ApoE4 positive group (Beta=1.2, p=0.04) was found. A statistically significant interaction between ApoE4 and prevalent CVD on Trails B-A time to completion ($p_{interaction}$=0.01) was observed and there was an inverse association between prevalent CVD and Trails B-A time to completion only among those in the ApoE4 negative group (Beta=−0.10, p=0.003).

### Interaction between ApoE4 Status and Cardiovascular Risk Factors on Error Response NP Outcome Measures

Table 4b shows the stratum-specific results for the statistically significant interactions between ApoE4 and the FSRP score and its components on the error response NP outcome measures.

There was an interaction between ApoE4 and age on each of Animals % perseverations ($p_{interaction}$=0.01), Animals % total errors ($p_{interaction}$=0.01), and Trails B total errors

($p_{interaction}$=0.006). For Animals % total errors and % perseverations, age had a larger absolute effect on the above-mentioned tests results among those with ApoE4 than among those without ApoE4. For example, a one year increment of age was associated with a 6 percent (p=0.0002) increase in odds of having Animals % perseverations ≥75$^{th}$ percentile (versus <75$^{th}$ percentile) among those with ApoE4 and only a 2 percent (p=0.03) increased odds of Animals % perseverations ≥75$^{th}$ percentile among those without ApoE4. However, age was associated with total Trails B errors only among those without the ApoE4 allele (OR=1.05, p<0.0001). A significant interaction was observed between ApoE4 and hypertension for FAS % total errors ($p_{interaction}$=0.04). However, the stratum-specific effects for each ApoE4 group were not statistically significant, so the interpretation of these interactions is not clear.

## Discussion

Our primary analyses revealed that higher midlife FSRP was associated with poorer performance on traditional measures of executive function from the tests of Animals fluency and Trails B (corrected for psychomotor speed and attention). For individual risk factors, increasing age was associated with executive dysfunction across all traditional measures. In the analysis of the individual FSRP components, the results were modest. Having diabetes 8 years earlier was associated with poorer performance on fluency tests and being a smoker resulted in a slower Trails B time. These results were consistent with previous research[10,38], and also reflect the lack of consensus of significant relationships between other CVRF and EF in clinically asymptomatic populations [6,8,9,11,13]. These differences likely stem from variations in study sample demographics [8–11], tests of EF [6,8–11], and varying years of follow-up, ranging from 4–20 years [9,11].

For the error response NP measures, error performance on Trails B (total errors and pen lifts) was related to the composite FSRP score. Interestingly, while FSRP was not related to the standard DS-B total score, higher FSRP was associated with making more errors on the test. Similarly, prevalent CVD was not related to any traditional NP measure, but was related to greater likelihood of making significantly more perseverations (e.g., > 75$^{th}$ percentile) on the FAS test.

ApoE4 status did have a modifying effect on the association between cardiovascular risk factors and several traditional cognitive test scores. Significant interactions between ApoE4 were found for the relationships between age and the total correct responses in Animal fluency, hypertension and both FAS and Animal fluency and prevalent CVD and Trails B. Stratified analyses suggested that the relationship was evident or exacerbated for those who were ApoE4+ for the outcomes of both fluency tests while, among those who were ApoE4−, prevalent CVD was associated with faster Trails B performance.

Again, novel to this study were results that emerged when looking at the modifying effects of ApoE4 on the relationships between midlife cardiovascular risk and error response EF measures. Also of note is that each of these significant findings was in the expected direction, where higher risk was associated with poorer performance for the overall interaction and within stratified analyses, ApoE4+ was associated with more exacerbated findings of perseverations and errors (e.g., Animal fluency test). However, the significance of these findings must be considered with caution because of the small number of errors that were made by this relatively healthy sample population and the lack of confirmatory clinical follow-up. However, the fact that these relationships could be detected using the error response measures, despite the low power, is of interest.

The findings suggest that the relationships between vascular risk factors and cognition are complex. ApoE4 has been associated with several pathological processes, including increased amyloid β deposition, and, separately, inefficient responses to central nervous system stressors (e.g. ischemia, inflammation)[39,40]. That the novel error response measures were linked to these changes in a pre-symptomatic, low cardiovascular risk population suggests a potential utility for their use. Furthermore, these findings could possibly demonstrate significant usefulness of the error response measures in providing early evidence of cognitive impairment to meet new diagnostic criteria for mild cognitive impairment and for preclinical research[17,18].

The strengths of this study include the community-based setting and the prospective design of cardiovascular risk measures at mid-life and cognitive measures 10–15 years later. The mid-life exposure may reflect chronicity and the cumulative impact of years of risk on cognition. These results support the potential clinical postulation that management of cardiovascular risk can reduce risk of poorer cognitive outcomes later in life. The study, however, has a number of limitations. The study participants are predominantly Caucasian, highly educated, and comparatively healthy (e.g., low average and restricted range of FSRP scores). Additionally, the cognitive measures are cross-sectional and measurements of change in cognitive measures over time are not available. Furthermore, since there was no adjustment for multiple comparisons, we cannot rule out the possibility that our results are due to false positives.

Of significance, however, is that even in this highly educated, low cardiovascular risk population, there were relationships between cardiovascular risk and novel measures of executive function, primarily amongst those subjects who are ApoE4 positive. Although more studies need to be done, the use of error response measures has important implications on methods for detecting cognitive changes at the earliest stages of the preclinical spectrum that current traditional measures do not.

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## References

1. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. Bmj. Jun 16; 2001 322(7300):1447–1451. [PubMed: 11408299]
2. Schnaider Beeri M, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. Neurology. Nov 23; 2004 63(10):1902–1907. [PubMed: 15557509]
3. Tyas SL, White LR, Petrovitch H, et al. Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. Neurobiol Aging. Jul-Aug;2003 24(4):589–596. [PubMed: 12714116]
4. Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. Jan 25; 2005 64(2):277–281. [PubMed: 15668425]
5. Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. Aug 23; 2005 65(4):545–551. [PubMed: 16116114]
6. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. Aug 2; 2011 77(5):461–468. [PubMed: 21810696]
7. Arntzen KA, Schirmer H, Wilsgaard T, et al. Impact of cardiovascular risk factors on cognitive function: the Tromso study. Eur J Neurol. May; 2011 18(5):737–743. [PubMed: 21143340]

8. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. Jan 9; 2001 56(1):42–48. [PubMed: 11148234]
9. Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology. Nov 8; 2011 77(19):1729–1736. [PubMed: 22067959]
10. Galanis DJ, Petrovitch H, Launer LJ, et al. Smoking history in middle age and subsequent cognitive performance in elderly Japanese-American men. The Honolulu-Asia Aging Study. Am J Epidemiol. Mar 15; 1997 145(6):507–515. [PubMed: 9063340]
11. Kilander L, Nyman H, Boberg M, et al. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension. Mar; 1998 31(3):780–786. [PubMed: 9495261]
12. Kilander L, Nyman H, Boberg M, et al. The association between low diastolic blood pressure in middle age and cognitive function in old age. A population-based study. Age Ageing. May; 2000 29(3):243–248. [PubMed: 10855907]
13. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. Jun 26; 2001 56(12):1683–1689. [PubMed: 11425934]
14. Launer LJ, Masaki K, Petrovitch H, et al. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. Jama. Dec 20; 1995 274(23): 1846–1851. [PubMed: 7500533]
15. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke. Nov; 1998 29(11):2334–2340. [PubMed: 9804644]
16. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. Jan 16; 2002 287(3):356–359. [PubMed: 11790215]
17. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May; 2011 7(3):270–279. [PubMed: 21514249]
18. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May; 2011 7(3):280–292. [PubMed: 21514248]
19. Caselli RJ, Reiman EM, Locke DE, et al. Cognitive domain decline in healthy apolipoprotein E epsilon4 homozygotes before the diagnosis of mild cognitive impairment. Arch Neurol. Sep; 2007 64(9):1306–1311. [PubMed: 17846270]
20. Knopman DS, Mosley TH, Catellier DJ, et al. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement. May; 2009 5(3):207–214. [PubMed: 19362884]
21. Whitehair DC, Sherzai A, Emond J, et al. Influence of apolipoprotein E varepsilon4 on rates of cognitive and functional decline in mild cognitive impairment. Alzheimers Dement. Sep; 2010 6(5):412–419. [PubMed: 20813342]
22. Blair CK, Folsom AR, Knopman DS, et al. APOE genotype and cognitive decline in a middle-aged cohort. Neurology. Jan 25; 2005 64(2):268–276. [PubMed: 15668424]
23. Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. Neurology. Jun; 1998 50(6):1580–1585. [PubMed: 9633697]
24. Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. Jama. Jul 7; 1999 282(1):40–46. [PubMed: 10404910]
25. Peila R, White LR, Petrovich H, et al. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. Stroke. Dec 1; 2001 32(12):2882–2889. [PubMed: 11739991]
26. Zade D, Beiser A, McGlinchey R, et al. Interactive effects of apolipoprotein E type 4 genotype and cerebrovascular risk on neuropsychological performance and structural brain changes. J Stroke Cerebrovasc Dis. Jul-Aug;2010 19(4):261–268. [PubMed: 20471857]

27. Qiu C, Winblad B, Fratiglioni L. Cerebrovascular disease, APOE epsilon4 allele and cognitive decline in a cognitively normal population. Neurol Res. Sep; 2006 28(6):650–656. [PubMed: 16945218]

28. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke. Mar; 1991 22(3):312–318. [PubMed: 2003301]

29. Feinleib M, Kannel WB, Garrison RJ, et al. The Framingham Offspring Study. Design and preliminary data. Prev Med. Dec; 1975 4(4):518–525. [PubMed: 1208363]

30. D'Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke. Jan; 1994 25(1):40–43. [PubMed: 8266381]

31. Llewellyn DJ, Lang IA, Xie J, et al. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. BMC Neurol. 2008; 8(12):12. [PubMed: 18430227]

32. Truelsen T, Lindenstrom E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. Stroke. Apr; 1994 25(4):802–807. [PubMed: 8160224]

33. Au R, Seshadri S, Wolf PA, et al. New norms for a new generation: cognitive performance in the framingham offspring cohort. Exp Aging Res. Oct-Dec;2004 30(4):333–358. [PubMed: 15371099]

34. Kaplan, EFD.; Morris, RG.; Delis, DC. The Weschler Adult Intelligence Scale - Revised as a Neuropsychological Instrument. San Antonio, TX: Psychological Corporation; 1991.

35. Libon DJ, Bondi MW, Price CC, et al. Verbal serial list learning in mild cognitive impairment: a profile analysis of interference, forgetting, and errors. J Int Neuropsychol Soc. Sep; 2011 17(5): 905–914. [PubMed: 21880171]

36. Bettcher BM, Giovannetti T, Macmullen L, et al. Error detection and correction patterns in dementia: a breakdown of error monitoring processes and their neuropsychological correlates. J Int Neuropsychol Soc. Mar; 2008 14(2):199–208. [PubMed: 18282318]

37. Hankee, LDPS.; Beiser, AS.; Devine, SA., et al. Experimental Aging Research. 2013. Qualitative Neuropsychological Measures: Normative Data on executive functioning tests from the Framingham Offspring Study. Accepted for Publication

38. Luchsinger JA, Reitz C, Patel B, et al. Relation of diabetes to mild cognitive impairment. Arch Neurol. Apr; 2007 64(4):570–575. [PubMed: 17420320]

39. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A. Apr 11; 2006 103(15):5644–5651. [PubMed: 16567625]

40. Wisniewski T, Castano EM, Golabek A, et al. Acceleration of Alzheimer's fibril formation by apolipoprotein E in vitro. Am J Pathol. Nov; 1994 145(5):1030–1035. [PubMed: 7977635]

## Table 1

Demographics, Risk Factor Characteristics, and Mean and SD Scores on Neuropsychological Tests at Baseline (1991–1995)

| | N = 1755 |
|---|---|
| **Mean (SD)** | |
| Age at NP battery | 67.2 (9.1) |
| Age at Exam 5 | 53.6 (9.1) |
| Time between exam 5 and NP battery (years) | 14.1 (1.2) |
| FSRP score | 3.6 (3.7) |
| MMSE score | 29.1 (1.2) |
| **n (%)** | |
| Female sex | 941 (53.6) |
| Education group | |
| < HS graduate | 60 (3.4) |
| HS graduate | 996 (56.8) |
| College graduate | 369 (21.0) |
| >College graduate | 330 (18.8) |
| ApoE4 Carriers | 364 (21.1) |
| Current Smoking | 287 (16.4) |
| Diabetes | 94 (5.4) |
| Hypertension | 476 (27.1) |
| Prevalent CVD | 83 (4.7) |
| Trails B early start | 108 (6.5) |
| **Mean (SD)** | |
| FAS – Number of correct responses | 37.8 (12.3) |
| Animals – Number of correct responses | 18.1 (5.1) |
| DS-B - Total score | 4.9 (1.3) |
| **Median ($25^{th}$, $75^{th}$ percentile)** | |
| FAS - % Perseverations | 2.6 (0.0, 5.7) |
| FAS - % Total errors | 4.7 (1.8, 9.1) |
| Animals - % Perseverations | 0.0 (0.0, 5.3) |
| Animals - % Total errors | 0.0 (0.0, 5.6) |
| Trails B-A –Time to completion (seconds) | 0.8 (0.5, 1.2) |
| Trails B – Total errors | 0.0 (0.0, 1.0) |
| Trails B – Number of penlifts | 1.0 (0.0, 2.0) |
| DS-B – Capacity score$^{\dagger}$ | 0.0 (0.0, 1.0) |
| DS-B - % Total errors | 42.9 (37.5, 55.6) |
| DS-B - % Sequencing errors | 25.0 (0.0, 33.3) |

Abbreviations: SD = standard deviation; NP = neuropsychological; MMSE = Mini-Mental State Examination; HS = high school; ApoE4 = apolipoprotein ε4; CVD = cardiovascular disease; AF = atrial fibrillation; DS-B=digit span backwards

† Difference between DS-B total and error response score

**Table 2**

Association between Midlife Cardiovascular Risk Factors and Traditional NP Outcome Measures.

| **Continuous Outcomes** | **Exposure** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **FSRP Score** | | **Age** | | **Sex** | | **Current Smoking** | | **Diabetes** | | **Hypertension** | | **Prevalent CVD** | |
| | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** | **Beta (SE)** | **P-value** |
| FAS – No. correct responses | −0.11 (0.10) | 0.27 | **−0.29 (0.03)** | **<0.0001** | **3.0 (0.56)** | **<0.0001** | −0.33 (0.75) | 0.66 | **−3.3 (1.2)** | **0.007** | −0.63 (0.65)* | 0.34 | −1.8 (1.3) | 0.17 |
| Animals – No. correct responses | **−0.09 (0.04)** | **0.03** | **−0.21 (0.01)*** | **<0.0001** | −0.32 (0.22) | 0.14 | −0.13 (0.30) | 0.67 | −0.96 (0.49) | 0.05 | −0.002 (0.26)* | 0.99 | −0.69 (0.52) | 0.18 |
| Trails B-A – Time to completion† | **−0.008 (0.002)** | **0.0002** | **−0.01 (0.0007)** | **<0.0001** | 0.02 (0.01) | 0.18 | −0.01 (0.02) | 0.44 | −0.0009 (0.03) | 0.97 | −0.02 (0.01) | 0.19 | −0.05 (0.03)* | 0.07 |
| DS-B – Total score | −0.01 (0.01) | 0.25 | **−0.01 (0.004)** | **0.0003** | 0.07 (0.07) | 0.28 | 0.039 (0.088) | 0.66 | −0.24 (0.15) | 0.09 | 0.046 (0.076) | 0.54 | 0.057 (0.15) | 0.71 |

Abbreviations: FSRP = Framingham Stroke Risk Profile; CVD = cardiovascular disease; OR = odds ratio; CI=confidence interval; SE=standard error; DS-B = Digit Span Backwards

Note: All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing. Sample size for each test is as follows: FAS (n=1706), Animals (n=1706), Trails B (n=1651), DS-B (n=1628).

† Log transformed

* Interaction with APOE genotype p<0.05

** Interaction with APOE genotype p<0.01

**Table 3**

Association between Midlife Cardiovascular Risk Factor and Error Response NP Outcome Measures

| Categorical Outcomes (≥75th vs <75th percentile) | Exposure | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FSRP Score | | Age | | Sex | | Current Smoking | | Diabetes | | Hypertension | | Prevalent CVD | |
| | OR (96% CI) | P-value | OR (96% CI) | P-value | OR (96% CI) | P-value | OR (96% CI) | P-value | OR (96% CI) | P-value | OR (96% CI) | P-value | OR (96% CI) | P-value |
| FAS - % Perseverations | 0.99 (0.95–1.03) | 0.65 | **1.04 (1.03–1.05)** | **<0.0001** | 0.82 (0.65–1.03) | 0.09 | 0.74 (0.53–1.04) | 0.08 | 0.75 (0.44–1.28) | 0.30 | 0.90 (0.69–1.18) | 0.46 | **0.51 (0.28–0.93)** | **0.03** |
| FAS - % Total Errors | 1.01 (0.97–1.05) | 0.73 | **1.04 (1.02–1.05)** | **<0.0001** | **0.70 (0.55–0.89)** | **0.003** | 1.29 (0.95–1.76) | 0.11 | 0.72 (0.42–1.23) | 0.22 | 1.01 (0.77–1.32)* | 0.93 | 0.79 (0.46–1.36) | 0.40 |
| Animals - % Perseverations | 1.00 (0.96–1.04) | 0.99 | **1.03 (1.01–1.04)*** | **0.0003** | **1.27 (1.01–1.60)** | **0.045** | 1.08 (0.79–1.47) | 0.64 | 0.62 (0.36–1.09) | 0.10 | 0.98 (0.75–1.29) | 0.89 | 1.48 (0.90–2.44) | 0.12 |
| Animals - % Total Errors | 0.98 (0.94–1.03) | 0.41 | **1.03 (1.02–1.05)*** | **<0.0001** | 1.23 (0.97–1.55) | 0.09 | 1.07 (0.78–1.47) | 0.66 | 0.57 (0.32–1.02) | 0.06 | 0.90 (0.69–1.19) | 0.47 | 1.46 (0.89–2.41) | 0.13 |
| Trails B - Total Errors | **1.05 (1.00–1.09)** | **0.04** | **1.04 (1.03–1.05)**** | **<0.0001** | 0.97 (0.79–1.19) | 0.76 | 0.97 (0.73–1.28) | 0.82 | 1.18 (0.75–1.86) | 0.48 | 1.05 (0.83–1.34) | 0.68 | 1.14 (0.70–1.84) | 0.60 |
| Trails B - No. of Penlifts | 1.04 (1.00–1.09) | 0.05 | **1.06 (1.05–1.07)** | **<0.0001** | 1.06 (0.85–1.32) | 0.64 | 0.99 (0.73–1.34) | 0.95 | 1.23 (0.76–1.96) | 0.40 | 1.23 (0.96–1.57) | 0.11 | 0.94 (0.57–1.54) | 0.80 |
| Trails B - Early Start (Y vs. N) | 0.93 (0.84–1.01) | 0.09 | **1.05 (1.02–1.07)** | **0.0001** | 1.05 (0.70–1.57) | 0.82 | 1.14 (0.66–1.98) | 0.64 | 0.57 (0.20–1.62) | 0.29 | 1.04 (0.66–1.62) | 0.88 | 0.72 (0.28–1.88) | 0.51 |
| DS-B - Capacity Score† | **1.05 (1.00–1.09)** | **0.03** | 1.01 (0.99–1.02) | 0.70 | 0.93 (0.75–1.16) | 0.32 | 0.96 (0.71–1.29) | 0.77 | 1.23 (0.76–1.98) | 0.41 | 1.03 (0.80–1.33) | 0.82 | 1.09 (0.66–1.80) | 0.74 |
| DS-B - % Total Errors | **1.05 (1.01–1.10)** | **0.02** | 1.00 (0.99–1.02) | 0.62 | 0.84 (0.66–1.07) | 0.15 | 1.07 (0.78–1.48) | 0.66 | 1.28 (0.76–2.14) | 0.35 | 1.03 (0.78–1.35) | 0.86 | 1.22 (0.72–2.08) | 0.46 |
| DS-B - % Sequencing Errors | 1.02 (0.98–1.06) | 0.35 | 1.00 (0.98–1.01) | 0.50 | 0.85 (0.68–1.05) | 0.13 | 1.07 (0.80–1.42) | 0.67 | 0.69 (0.41–1.17) | 0.17 | 1.08 (0.84–1.39) | 0.57 | 0.90 (0.54–1.51) | 0.70 |

Abbreviations: FSRP = Framingham Stroke Risk Profile; CVD = cardiovascular disease; OR = odds ratio; CI=confidence interval, DS-B = Digit Span Backwards

All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing.

† Difference between DS-B total and error response score

* Interaction with APOE4 genotype p<0.05

** Interaction with APOE4 genotype p<0.05

**Table 4a**

Statistically Significant Interactions between ApoE4 and Midlife Cardiovascular Risk Factor Exposure on Traditional NP Outcome Measures (P-value<0.05)

| Continuous Outcomes | Exposure | ApoE4− (N=1359) | | ApoE4+ (N=364) | | P-value for Interaction |
|---|---|---|---|---|---|---|
| | | Beta (SE) | P-value | Beta (SE) | P-value | |
| FAS – No. total responses | Hypertension | 0.10 (0.74) | 0.89 | −3.2 (1.4) | 0.03 | 0.04 |
| Animals – No. correct responses | Age | −0.20 (0.01) | <0.0001 | −0.26 (0.03) | <0.0001 | 0.03 |
| | Hypertension | −0.25 (0.29) | 0.39 | 1.2 (0.58) | 0.04 | 0.03 |
| Trails B-A – Time to completion† | Prevalent CVD | −0.10 (0.03) | 0.003 | 0.07 (0.06) | 0.21 | 0.01 |

Abbreviations: OR = odds ratio; CI=confidence interval; SE=standard error; ApoE4− = apolipoprotein ε4 negative group; ApoE4+ = apolipoprotein ε4 positive group;

All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing.

†Log transformed

**Table 4b**

Statistically Significant Interactions between ApoE4 and Midlife Cardiovascular Risk Factors on Error Response NP Outcome Measures (P-value<0.05)

| Categorical Outcomes (≥75th vs <75th percentile) | Exposure | ApoE4− (N=1359) | | ApoE4+ (N=364) | | P-value for Interaction |
|---|---|---|---|---|---|---|
| | | OR (95% CI) | P-value | OR (95% CI) | P-value | |
| FAS - % Total errors | Hypertension | 0.86 (0.64–1.15) | 0.30 | 1.68 (0.93–3.03) | 0.08 | 0.04 |
| Animals - % Perseverations | Age | 1.02 (1.00–1.03) | 0.03 | 1.06 (1.03–1.10) | 0.0002 | 0.01 |
| Animals - % Total Errors | Age | 1.02 (1.01–1.04) | 0.004 | 1.07 (1.03–1.10) | <0.0001 | 0.01 |
| Trails B - Total Errors | Age | 1.05 (1.03–1.06) | <0.0001 | 1.01 (0.98–1.03) | 0.63 | 0.006 |

Abbreviations: OR = odds ratio; CI=confidence interval; ApoE4− = apolipoprotein ε4 negative group; ApoE4+ = apolipoprotein ε4 positive group;

All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing.